REMARKS

A. Status of the Claims

Claims 63-74 are currently pending. Claims 64 and 68-70 are withdrawn, claims 63, 65-67, and 71 stand rejected, and claims 72-74 are objected to as depending from non-allowed claims.

B. Rejection under 35 USC §103 - Obviousness

Claims 63, 65, and 67 stand rejected as allegedly obvious in view of Michnick et al. ("Michnick"), in view of Blau et al. ("Blau") and Pieper et al. ("Peiper"). Claims 63, 65, 66, and 71 stand rejected as allegedly obvious in view of Michnick et al., in view of Blau et al., Pieper et al., Moore et al. ("Moore"), and Maveyraud et al. ("Maveyraud").

Applicants respectfully disagree because none of the cited reference teach or suggest a fragment complementation system in which the N-terminal and C-terminal fragments are covalently bonded ***through the Class A β-lactamase break point*** to the respective interactor domains. Moreover, one skilled in the art would not be motivated to modify the teachings of the cited references to arrive at Applicants' invention. Even if such a motivation were present, one skilled in the art would not have a reasonable expectation of successfully modifying the cited references to arrive at an operable fragment complementation system.

1. Burden of Proof in Establishing Prima Facie Obviousness

"The examiner bears the burden of establishing a *prima facie* case of obviousness. *In re Rijckaert*, 9 F.3d 1531, 1532, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993); *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). Only if this burden is met does the burden of coming forward with rebuttal arguments or evidence shift to the applicant. *Rijckaert*, 9 F.3d at 1532, 28 USPQ2d at 1956. When the references cited by the examiner fail to establish a *prima facie* case of obviousness, the rejection is improper and will be overturned. *In re Fine*, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988)." See *In re Deuel*, 51 F.3d 1552, 34 USPQ2d 1210, 1214 (Fed. Cir. 1995).

In order to establish a *prima facie* case of obviousness, the rejection must demonstrate that (1) the cited references teach all the claimed elements; (2) there is a suggestion or motivation in the prior art to modify or combine the reference teachings; and (3) there is a reasonable expectation of success. MPEP § 2143; *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991). As explained below, Applicants submit that the cited references do not provide a suggestion or motivation to combine the references and fail to provide a basis for one of skill to reasonably expect that Applicants' methods would be useful in delivering a pharmaceutical agent to the blood brain barrier.

The Federal Circuit has recently held that "[m]ost if not all inventions arise from a combination of old elements...Thus, every element of a claimed invention may often be found in the prior art...However, identification in the prior art of each individual part claimed is insufficient to defeat patentability of the whole claimed invention...Rather, to establish obviousness based upon a combination of the elements disclosed in the prior art, there must be some motivation, suggestion or teaching of the desirability of making the specific combination that was made by the applicant." *See In Re Kotzab*, 217 F.3d 1365, 1369-1370 (Fed.Cir. 2000)(citations omitted)

In addition to suggesting or motivating one of ordinary skill in the art to combine the prior art to make the claimed invention, the prior art must also have taught that such a combination would have a "reasonable expectation of success." *In re Vaeck*, 947 F.2d 488, 493 (Fed.Cir. 1991). "'Obvious to try' has long been held not to constitute obviousness." *In re Deuel*, 51 F.3d 1552, 1559 (Fed.Cir. 1995).

2. The Art of Record Fails to Teach Each Claim Element

Applicants were the first to discover a functional fragment complementation system having N-terminal and C-terminal Class A β-lactamase fragments ***fused through the enzyme break points*** to the respective interactor domains. None of the prior art references teach or suggest a fragment complementation system in which the N-terminal and C-terminal fragments of ***any enzyme*** are fused through the enzyme break points, much less a Class A β-lactamase enzyme.

Michnick describes a protein-fragment complementation assay (PCA) using murine dihydrofolate reductase protein fragments (DHFR), in which "(r)econstitution of activity ***only*** occurred when both N- and C-terminal fragments of DHFR were coexpressed as ***C-terminal fusions*** to GCN4 leucine zipper sequences ...." See Col. 5, lines 8-12 (emphasis added). In fact, Michnick's "general description" of PCA is limited to systems in which "the chosen fragments are subcloned, and ***to the 5' ends of each***, proteins that either are known or thought to interact are fused." See Michnick et al., Col. 4, lines 27-72 (emphasis added). Therefore, Michnick does not teach or suggest a fragment complementation system in which the N-terminal and C-terminal fragments of any enzyme are fused to the interactor domains through the enzyme break points.

Blau also fails to teach or suggest a functional fragment complementation system having N-terminal and C-terminal Class A β-lactamase fragments fused through the enzyme break points to the respective interactor domains. For example, Blau describes the construction of β-galactose fragments in which the interactor domains (FKBP12 and FRAP) are fused through the N-termini of the β-galactose fragments. See page 35, lines 25-36 and Figure 2B. A similar construction is shown in Figure 7B using EGFR domains.

Like Blau and Michnick, Pieper does not teach or suggest fusion through an enzyme break point. In fact, Pieper fails to disclose fusion of an enzyme fragment to any interactor domain. Moreover, Peiper discloses a uni-molecular circularly-permutated β-lactamase, not a complementation system containing two separate oligopeptides capable of functionally reconstituting. Therefore, not only does Peiper fail to teach or suggest fusion through an enzyme break point, Peiper is irrelevant to Applicants' claimed fragment complementation system that includes two separate oligopeptides capable of functionally reconstituting.

Moore and Maveyraud fail to cure the defects of Blau, Michnick and Peiper as Moore and Maveyraud are merely cited for the proposition that "TEM-1 β-lactamase is a good reporter." See Official Action dated June 27, 2005 at page 12.

Therefore, because none of the cited reference disclose a functional fragment complementation system having N-terminal and C-terminal Class A β-lactamase fragments fused

through the enzyme break points to the respective interactor domains, Applicants respectfully request withdrawal of the rejection.

3. There is No Motivation in the Prior Art to Modify the Referenced Fusion Constructs

Even if the cited references disclosed all the elements of the claimed invention, there is no motivation provided in the prior art to modify the referenced fusion constructs to arrive at Applicants' invention. The cited references do not disclose any deficiency in the reported constructs that would motivate one skilled in the art to fuse the fragments through the enzyme break point. In fact, the only motivation to modify the referenced fusion constructs is provided in Applicants' disclosure. To establish a proper *prima facie* case of obviousness, however, the teaching or suggestion to make a proposed modification to the prior art must be found in the prior art, not in Applicants' disclosure.

Because there is no motivation provided in the prior art to modify the referenced fusion constructs to arrive at Applicants' invention, withdrawal of the rejection is respectfully requested.

4. There is No Reasonable Expectation of Successfully Modifying the Referenced Constructs to Arrive at Applicants' Invention

Assuming *arguendo* that the other basic elements of a *prima facie* case have been set forth, the cited references fail to provide a reasonable expectation of success. There is no indication in the prior art that the orientation of the referenced fragment fusion constructs may be reversed to arrive at an operable complementation system. As noted by Michnick, orientation of the fragments is important in the design protein complementation assays. See Michnick at Col. 3, line 58, to Col. 4, line 9.

Because the prior art provides no expectation of successfully modifying the referenced constructs to arrive at Applicants' invention, withdrawal of the rejection is respectfully requested.

C. Double Patenting Rejection

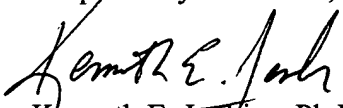
The Examiner has rejected claims 63, 65-67 and 71 under the judicially created obviousness-type double patenting as allegedly unpatentable over claims 63-65 of U.S. Patent Application No. 09/526,106 in view of Michnick and Blau. Claims 63, 65-67 and 71 stand rejected under the judicially created obviousness-type double patenting as allegedly unpatentable over claims 1, 12, and 13 of U.S. Patent Application No. 10/330,811.

Applicants request that the rejection be held in abeyance until allowable subject matter is found, at which time Applicants' will take the necessary steps to obviate the rejection.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are nonobvious over the cited references. The withdrawal of all obviousness rejections is respectfully requested.

Respectfully submitted,



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